New Yeast Trick for Eating Favorite Food

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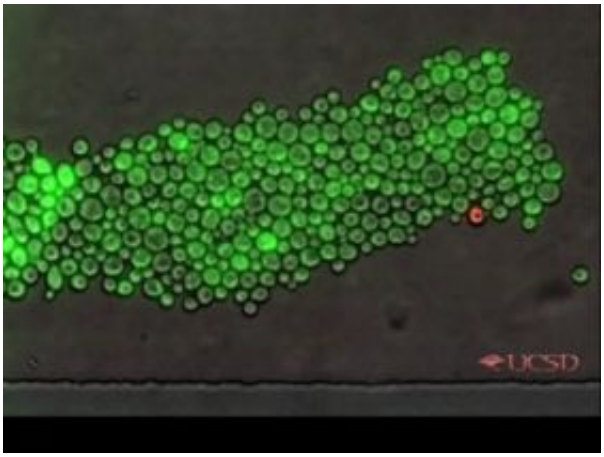

Microscope imagery of yeast growing in a microfluidic chamber specially designed to control the sugars the yeast have access to. Credit: UC San Diego Jacobs School of Engineering

It is well known that yeast, the humble ingredient that goes into our breads and beers, prefer to eat some sugars more than others. Glucose, their favorite food, provides more energy than any other sugar, and yeast has evolved a complex genetic network to ensure that they consume as much glucose as possible whenever it is available. UC San Diego bioengineers have recently identified a previously unknown mechanism that allows yeast to shut down the metabolism of another sugar, galactose, when they sense glucose in the environment.

The findings will be published online by the journal *Nature* on 30 July 2008. Narrated video of yeast growing in the experimental conditions is

available at:
http://video-jsoe.ucsd.edu/asx/Hasty_Nature_Yeast_7_2008.wmv.asx
(Internet Explorer on a PC works best)

This research marks the first discovery of post-transcriptional gene regulation in a key model for gene regulation in higher organisms: the galactose genetic system in the yeast Saccharomyces cerevisiae.

Molecular biologists have long thought that the primary mechanism for regulating genes is through proteins called transcription factors, which can either increase or decrease the activity of a gene by binding directly to the DNA. However, a paradigm shift has occurred in recent years as researchers have shown that the control of genes frequently occurs at the intermediated stages between transcription and the formation of functional proteins. This "post-transcriptional" regulation provides cells with an additional level of control over phenotypic expression.

The UCSD team demonstrated that the glucose network actively shuts down the galactose network by degrading messenger RNA that would otherwise go on to form the enzymes needed to metabolize galactose.

"To find something new in the well-known galactose network after predicting it is extremely exciting," said Matthew Bennett, the first author on the Nature paper and a postdoctoral researcher in the Systems Biodynamics Lab in UC San Diego's bioengineering department.

A better understanding of the yeast galactose network could lead to new insights in human cell behavior, human physiology and metabolic diseases such as diabetes. "The more we know about gene networks, the more we learn about how they can fail," said Bennett.

Feeding Yeast the Microfluidic Way

The work also highlights the kinds of important biological insights that scientists can gain by studying how gene networks operate in dynamic, life-like environments, rather than in steady-state environments. The bioengineers built yeast growth chambers in which food is delivered by microfluidic tubes. The design allowed for the raising and lowering of glucose levels with great control, while keeping galactose levels steady.

"Much of gene regulation appears to deal with changes in the environment. Our new work demonstrates that you can modify the environment in a highly controlled way and then monitor single cells in order to see how specific gene networks respond to the environmental changes," explained bioengineering professor Jeff Hasty, the senior author on the Nature paper.

The researchers found that yeast are much better at adapting to changes in available food sources than the prevailing models predicted.

"We didn't expect that yeast would respond so quickly to changes in glucose levels until we did these experiments," said Bennett

By controlling the exact growth conditions with microfluidic technology, the engineers determined that the canonical models for the yeast metabolic network underestimated how quickly and nimbly yeast can switch from galactose to glucose.

"The experimental system was much better than the computational models predicted. The model started filtering out the glucose pulses too soon," said Hasty, who stressed the utility of their tried-and-true engineering approach. "We drove our system with a sine wave in typical engineering fashion, and sure enough, we learned something interesting."

The undulating sine wave represents pulses of glucose delivered to the yeast cells while galactose levels remained constant.

When the glucose pulses started coming faster and faster, the model underestimates the ability of the yeast to react to the glucose pulse by shutting down the galactose metabolic network.

This discrepancy between the experimental results and the model predictions got the bioengineers thinking about what could be happening that is not captured in the current model. A combination of computational modeling and experimental work led the researchers to a new post-transcriptional control mechanism in which jumps in glucose increase the degradation rate of messenger RNA that are crucial for the functioning of the galactose metabolic network.

Source: University of California - San Diego